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This e-newsletter presents reviews of important, recently published scientific articles selected by The North American Menopause Society (NAMS), the leading nonprofit scientific organization dedicated to improving women's health and quality of life through an understanding of menopause. Each has a commentary from a recognized expert that addresses the clinical relevance of the item. Oversight for this e-newsletter issue was by Peter F. Schnatz, DO, Chair, 2009-2010 NAMS Professional Education Committee. Opinions expressed in the commentaries are those of the authors and are not necessarily endorsed by NAMS or Dr. Schnatz. Disclosures are available on request. Past issues of this e-newsletter may be viewed on the NAMS Web site (www.menopause.org/news.html).

Aspirin use after colorectal cancer

Chan AT, Ogino S, Fuchs CS. Aspirin use and survival after diagnosis of colorectal cancer. *JAMA* 2009;302:649-658. **Level of evidence: II-2.**

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CONTEXT: Aspirin reduces risk of colorectal neoplasia in randomized trials and inhibits tumor growth and metastases in animal models. However, the influence of aspirin on survival after diagnosis of colorectal cancer is unknown. **OBJECTIVE:** To examine the association between aspirin use after colorectal cancer diagnosis on colorectal cancer-specific and overall survival. **DESIGN, SETTING, AND PARTICIPANTS:** Prospective cohort study of 1279 men and women diagnosed with stage I, II, or III colorectal cancer. Participants were enrolled in 2 nationwide health professional cohorts in 1980 and 1986 prior to diagnosis and followed up through June 1, 2008. **MAIN OUTCOME MEASURE:** Colorectal cancer-specific and overall mortality. **RESULTS:** After a median follow-up of 11.8 years, there were 193 total deaths (35%) and 81 colorectal cancer-specific deaths (15%) among 549 participants who regularly used aspirin after colorectal cancer diagnosis, compared with 287 total deaths (39%) and 141 colorectal cancer-specific deaths (19%)

among 730 participants who did not use aspirin. Compared with nonusers, participants who regularly used aspirin after diagnosis experienced a multivariate hazard ratio (HR) for colorectal cancer-specific mortality of 0.71 (95% confidence interval [CI], 0.53-0.95) and for overall mortality of 0.79 (95% CI, 0.65-0.97). Among 719 participants who did not use aspirin before diagnosis, aspirin use initiated after diagnosis was associated with a multivariate HR for colorectal cancer-specific mortality of 0.53 (95% CI, 0.33-0.86). Among 459 participants with colorectal cancers that were accessible for immunohistochemical assessment, the effect of aspirin differed significantly according to cyclooxygenase 2 (COX-2) expression (P for interaction = .04). Regular aspirin use after diagnosis was associated with a lower risk of colorectal cancer-specific mortality among participants in whom primary tumors overexpressed COX-2 (multivariate HR, 0.39; 95% CI, 0.20-0.76), whereas aspirin use was not associated with lower risk among those with primary tumors with weak or absent expression (multivariate HR, 1.22; 95% CI, 0.36-4.18). **CONCLUSION:** Regular aspirin use after the diagnosis of colorectal cancer is associated with lower risk of colorectal cancer-specific and overall mortality, especially among individuals with tumors that overexpress COX-2.

Comment. The concept of using aspirin to prevent cancer dates back to the 1970s when higher levels of prostaglandins were observed in tumors from the colon, breast, and lung. The venous blood draining from these tumors had higher levels of prostaglandins when the tumors were large or invasive. Many experiments were done with a variety of nonsteroidal agents (but with higher doses than those used for patient care) to determine whether they would chemically inhibit the growth and size of chemically induced tumors in rodents. Although these chemically induced tumors did not metastasize to the same degree as human tumors, these studies provided the foundation for further experimental study for colon cancer.

Aspirin is an inhibitor of COX-mediated prostaglandin synthesis. The COX-1 enzyme governs the production of physiologically important prostaglandins (blood flow and hemodynamics) and gastric mucosal protection (gastric blood flow, regulation of acid, nitric oxide, and mucus secretion) while the COX-2 enzyme is amplified during inflammatory reactions and governs the production of inflammation-related prostaglandins. In cells such as platelets, where there is no capacity to renew the COX-1 enzyme, aspirin blocks the production of prostaglandin for the life of the platelet. This forms the basis for the antithrombotic cardioprotective action of aspirin. The effects of aspirin on COX-2 result in products that have anti-inflammatory properties. Although COX-1 is a constitutive component of cells, COX-2 is induced in colon cancer cells and multiple studies have shown that a large proportion of colon cancer cells express COX-2 on the surface. Selective COX-2 inhibitors were developed because of the severe gastrointestinal (GI) side effects of aspirin.

There was a hope that these specific COX-2 inhibitors might prevent the formation of premalignant colonic adenomas. COX-2 inhibitors, however, were found to have serious side effects. For example, celecoxib showed an increase in the risk of serious cardiovascular events in a dose-related fashion when used in a

trial for colorectal adenoma prevention, and early discontinuation of the drug was recommended. Aspirin is an inhibitor of COX-2 expression at low doses and therefore aspirin was considered a good candidate medication for so-called chemoprevention against colon cancer.

The Women's Health Initiative showed no benefit for the women enrolled in taking aspirin *prior* to diagnosis—that is, it was not chemoprotective for *prevention* of the initial cancer. The Physicians' Health Study showed the same effect. In the United Kingdom, however, the British Doctors Aspirin Trial and the United Kingdom Transient Ischemic Attack Aspirin Trial demonstrated a significant reduction in risk for colorectal cancer. The difference between these studies is thought to be related to the dose of aspirin used. In the US trials, the doses were 50 mg and 162.5 mg daily, whereas the UK doses were 500 mg and 300 mg to 1,200 mg daily.

Chan et al reports that, for patients who have had colon cancer, aspirin is chemoprotective *after* the diagnosis has been made. These authors evaluated the effect of long-term aspirin use among patients who were enrolled in the Nurse's Health Study and the Health Professionals Follow-up Study. They obtained specimens from 76% of stage I, II, and III colon cancer cases over 16 years of follow-up in one trial and 58% of cases from a second trial. They analyzed COX expression on these tumors. In a prior evaluation, they had found that colorectal cancer risk was reduced for COX-2 positive tumors but not COX-2 negative tumors. In this study, the benefit of aspirin use after diagnosis appeared to be confined to those persons with COX-2 positive primary tumors. They also looked at whether survival was improved with aspirin treatment after diagnosis and found that decreased mortality was associated with COX-2 expression as well.

These patients were not asked to take aspirin—their use was determined by self-reporting on a

questionnaire, thus it was not a prospective, randomized, double-blinded trial. Interestingly, among those patients who took aspirin before their cancer diagnosis, continuation of the aspirin did not improve their longevity. The authors determined that regular aspirin use after the diagnosis of colorectal cancer is associated with decreased recurrence.

Do these studies represent the population at large, meaning can we translate this information into daily use for our patients? The populations tested were professionals who had been participating in a long-term study and had been evaluated prior to the study for their cooperation within the guidelines of the study. Aspirin is not a benign medication. There are significant potential GI tract consequences with long-term aspirin use such as bleeding, strictures, dyspepsia, and colitis. These findings are not confined to the gastric mucosa but can be found throughout the GI tract. At least 10% to 20% of patients who use NSAIDs develop symptoms. The studies that have evaluated the effect of aspirin on the development of colon cancer have lasted for as long as 20 years. The long study period was related to the long time interval for development of adenomas under the traditional adenoma-carcinoma sequence, up to 10 years. So, using aspirin for chemotherapy commits patients to many years of potential GI complications.

It is recommended before starting long-term treatment with aspirin or an NSAID that cardiovascular and GI risks should be stratified (see the excellent review by Gupta and Eisen 2009¹). If the patient is positive for *H. pylori*, then this should be treated first with antibiotics and a proton-pump inhibitor. Then cardiovascular risk is assessed. If low, a traditional NSAID can be started and if the patient becomes symptomatic a proton-pump inhibitor can be added. Increasing the dose increases the risk of an adverse event with older persons being at highest risk.

Sulindac, which primarily inhibits COX-2, has been approved by the Food and Drug

Administration for patients who have familial adenomatous polyposis as studies have shown that this medication reduces the number and size of adenomatous polyps in patients who have had total colectomy with ileorectal anastomosis. Higher-grade polyposis was also significantly decreased.

There has been a second pathway to colorectal cancer that was first described in the early 1990s that is related to serrated adenomas. These polyps are often found on the right side of the colon, more often in women, and grow more rapidly in comparison with the traditional adenoma. A total of 100% of these tumors are reported to express gastric mucin-related MUC6.² It would have been interesting to know whether the colorectal cancers that did not respond to aspirin were of this group. Serrated adenomas may have BRAF mutations, a high degree of microsatellite instability, and widespread promoter methylation. This latter group has an inverse relationship with COX-2 overexpression and would not be expected to respond to treatment with aspirin, so perhaps COX-2 inhibition may not play as large a role in the early stages of polyp formation in the serrated pathway. Although the number of studies is limited, one study on rectal cancer versus colon cancer showed that there was a strong inverse relationship between COX-2 expression and rectal cancer in Caucasians and a very weak inverse relationship for African Americans.³ African Americans are more likely to develop colon cancer and their mortality is higher, so this is a very interesting finding. It would also be expected that these neoplasms would not respond to COX-2 inhibition in the early stages of tumorigenesis. More information is needed about the molecular characteristics of these tumors.

In summary, we certainly do not have a magic bullet yet to prevent colon cancer by chemotherapy. The success rate of using aspirin is less than 50% for protection from colon cancer. We do have some tempting glimpses into what might be possible if suitable agents are developed. One such is a nitric oxide (NO)–

donating modification of aspirin, NCX 4016. This novel NO-donating NSAID holds promise of overcoming the limitations of the traditional nonsteroidals. Aspirin with a covalently attached NO moiety is 1,000 times more effective in inhibiting cell growth than aspirin alone in the prevention of colon cancer. The NO protects gastric mucosa from aspirin injury by reducing microvascular ischemia and sustaining defense mechanisms and leads to decreased risk of upper GI bleeding. This has been true for both in vivo and in vitro studies. In animals, NCX 4016 has been shown to be both safe and effective in cirrhosis, arthritis, diabetes, and older animals.⁴ NO-aspirin is already being tested in clinical trials.

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SHBG to predict diabetes

Ding EL, Song Y, Manson JE, et al. Sex hormone-binding globulin and risk of type 2 diabetes in women and men. *N Engl J Med* 2009;361:1152-1163. **Level of evidence: II-2.**

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BACKGROUND: Circulating sex hormone-binding globulin levels are inversely associated with insulin resistance, but whether these levels can predict the risk of developing type 2 diabetes is uncertain. **METHODS:** We performed a nested

case-control study of postmenopausal women in the Women's Health Study who were not using hormone therapy (359 with newly diagnosed type 2 diabetes and 359 controls). Plasma levels of sex hormone-binding globulin were measured; two polymorphisms of the gene encoding sex hormone-binding globulin, SHBG, that were robustly associated with the protein levels were genotyped and applied in mendelian randomization analyses. We then conducted a replication study in an independent cohort of men from the Physicians' Health Study II (170 with newly diagnosed type 2 diabetes and 170 controls). **RESULTS:** Among women, higher plasma levels of sex hormone-binding globulin were prospectively associated with a lower risk of type 2 diabetes: multivariable odds ratios were 1.00 for the first (lowest) quartile of plasma levels, 0.16 (95% confidence interval [CI], 0.08 to 0.33) for the second quartile, 0.04 (95% CI, 0.01 to 0.12) for the third quartile, and 0.09 (95% CI, 0.03 to 0.21) for the fourth (highest) quartile ($P < 0.001$ for trend). These prospective associations were replicated among men (odds ratio for the highest quartile of plasma levels vs. the lowest quartile, 0.10; 95% CI, 0.03 to 0.36; $P < 0.001$ for trend). As compared with homozygotes of the respective wild-type allele, carriers of a variant allele of the SHBG single-nucleotide polymorphism (SNP) rs6259 had 10% higher sex hormone-binding globulin levels ($P = 0.005$), and carriers of an rs6257 variant had 10% lower plasma levels ($P = 0.004$); variants of both SNPs were also associated with a risk of type 2 diabetes in directions corresponding to their associated sex hormone-binding globulin levels. In mendelian randomization analyses, the predicted odds ratio of type 2 diabetes per standard-deviation increase in the plasma level of sex hormone-binding globulin was 0.28 (95% CI, 0.13 to 0.58) among women and 0.29 (95% CI, 0.15 to 0.58) among men, a finding that suggests that sex hormone-binding globulin may have a causal role in the risk of type 2 diabetes. **CONCLUSIONS:** Low circulating levels of sex hormone-binding globulin are a strong predictor of the risk of type 2 diabetes in women and men. The clinical

usefulness of both SHBG genotypes and plasma levels in stratification and intervention for the risk of type 2 diabetes warrants further examination.

Comment. Ding et al provide a fascinating study looking at the potential ability of SHBG to predict development of type 2 diabetes mellitus (DM). We have had recent clues that circulating SHBG-bound sex steroids may be active at the tissue level, not just passively carried. The connection of how sex steroids (androgens and estrogens) and proteins may interact to affect chronic disease is very intriguing and has long been questioned. The authors used a sophisticated genetic analysis to try to discern if specific genetic variant alleles for SHBG types are more or less predictive of how SHBG in general may be potentially important in determining onset of DM. The sophisticated analysis and modeling were applied using some important assumptions. We are somewhat at the mercy of the analyses given the sophistication. It is exciting when population data can be analyzed using sophisticated techniques, newer genetic analyses, and newer biological insights. It has long been of interest, for example, why oral estrogen may be associated with lower risk of DM yet higher risk of thrombotic disorders when given to postmenopausal women, etc. Understanding some of these mechanisms in time might help us begin to understand these observations. The authors point out some potential limitations: First, the statistical power, with fewer than 600 newly diagnosed cases in the two cohorts, may be relatively limited, especially with regard to the genetic associations observed. Although residual confounding, particularly by adiposity, is possible with conventional observational analysis of biomarkers, this seemed unlikely to the authors. Another curious finding is that risk of DM for women is lower in the third quartile versus the fourth quartile. This is unlike what is reported for men and seems inconsistent with the authors' hypothesis. I wonder if this was an error of publication.

Please note also that the women with DM were more likely to be hypertensive, heavier, smokers,

younger when pregnant (a state of insulin resistance), have a strong family history of DM, and do less strenuous exercise. All of these factors can be associated with lower SHBG. Adjusting for all of this statistically can be difficult. The practicality of measuring SHBG in predicting DM versus well-known risk factors remains to be determined. Nonetheless, this report is a creative and sophisticated analysis and sets up further research as to why SHBG may be important in how androgens or estrogens might affect risk of chronic disease.

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Estrogen exposure time and coronary artery disease

Merz CN, Johnson BD, Berga SL, et al, for the Women's Ischemia Syndrome Evaluation Study Group. Total estrogen time and obstructive coronary disease in women: insights from the NHLBI-sponsored Women's Ischemia Syndrome Evaluation (WISE). *J Womens Health (Larchmt)* 2009;18:1315-1322. **Level of evidence: II-2.**

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OBJECTIVE: It has been suggested that both endogenous reproductive hormones and hormone therapy may play a protective role against coronary artery disease (CAD). However, recent clinical trials have failed to demonstrate the benefit of a variety of forms of hormone therapy. The observational data on the role of endogenous reproductive hormones, using surrogate measures such as number of birth, age at menarche, and age at menopause are inconsistent. In addition, the longer-term associations have not been evaluated. The aim of this study was to evaluate the relationships between detailed measurements of endogenous and exogenous estrogen exposure time with angiographic CAD and major adverse

cardiovascular events. **METHODS:** We assessed total estrogen exposure time, quantitative CAD by a core angiography laboratory, and prospectively measured major adverse cardiovascular events in 646 postmenopausal women undergoing coronary angiography for evaluation for suspected ischemia in the Women's Ischemia Syndrome Evaluation (WISE) study. **RESULTS:** Timing of postmenopausal exogenous hormone therapy (HT) use was associated with reduced CAD. Two summarized total estrogen time scores (TET and sTET) were not related to angiographic CAD after accounting for HT use. In addition, these scores were not related to cardiovascular events over a median of 6.0 years of follow-up. **CONCLUSIONS:** There was no independent relation of estrogen exposure time to angiographic CAD or major adverse cardiovascular events in a contemporary cohort of postmenopausal women evaluated for suspected ischemia. Our results suggest that the paradigm of estrogen protection from CAD in women may be more complex than estrogen exposure duration alone.

Comment. Whether endogenous estrogen exposure has an impact on later CAD in women is of great interest. This article reports that longer or shorter exposure to estrogens made by the ovary or from birth control pills or pregnancy did not impact the risk of CAD. The only positive finding was that menopausal hormone therapy (HT) reduced the risk of CAD significantly.

The study subjects were all women who had chest pain thought to be due to CAD and were referred for coronary angiography. Therefore, it is still not clear whether total estrogen exposure has an impact in the "normal" population. Further study with noninvasive techniques such as coronary calcification scores by electron beam computed tomography or rapid computerized tomography scan could explore this issue. In an unselected population in the Women's Health Initiative, testing by imaging coronary artery calcification was able to show less calcification of the coronaries in those women who were on estrogen-alone therapy (ET).¹ This technique

could be used in a normal population group as it is not invasive.

The study group included women with diabetes mellitus (DM). It is already known that these women are not protected during perimenopause or by postmenopausal ET. In fact, they have early CAD possibly more so than men. There were more women with DM in the CAD group. The group with CAD had more menopausal symptoms than the group without CAD. This suggests that the women with CAD would more likely be given HT, confounding the data.

At the present time, there is no plausible, known protective effect of early puberty on risk for CAD. The only known pubertal effects are that women who have polycystic ovarian syndrome are at higher risk as many of them develop metabolic syndrome and many have insulin resistance. Studies of lipids in puberty only show worsening in boys.² Perhaps excluding the years of puberty by using years of estrogen exposure after adulthood, perhaps after age 20, might have shown an effect. Early menopause and early oophorectomy have been shown to increase the risk of CAD in women under age 55.³

To completely resolve this issue, further exploration appears necessary in other population groups or by calculation of this type in even larger groups of women.

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Effect of exercise and diet on Alzheimer's disease

Scarmeas N, Luchsinger JA, Schupf N, et al. Physical activity, diet, and risk of Alzheimer disease. *JAMA* 2009;302:627-637. **Level of evidence: II-2.**

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CONTEXT: Both higher adherence to a Mediterranean-type diet and more physical activity have been independently associated with lower Alzheimer disease (AD) risk but their combined association has not been investigated.

OBJECTIVE: To investigate the combined association of diet and physical activity with AD risk. **DESIGN, SETTING, AND PATIENTS:**

Prospective cohort study of 2 cohorts comprising 1880 community-dwelling elders without dementia living in New York, New York, with both diet and physical activity information available. Standardized neurological and neuropsychological measures were administered approximately every 1.5 years from 1992 through 2006. Adherence to a Mediterranean-type diet (scale of 0-9; trichotomized into low, middle, or high; and dichotomized into low or high) and physical activity (sum of weekly participation in various physical activities, weighted by the type of physical activity [light, moderate, vigorous]; trichotomized into no physical activity, some, or much; and dichotomized into low or high), separately and combined, were the main predictors in Cox models. Models were adjusted for cohort, age, sex, ethnicity, education, apolipoprotein E genotype, caloric intake, body mass index, smoking status, depression, leisure activities, a comorbidity index, and baseline Clinical Dementia Rating score. **MAIN OUTCOME MEASURE:** Time to incident AD. **RESULTS:** A total of 282 incident AD cases occurred during a mean (SD) of 5.4 (3.3) years of follow-up. When considered simultaneously, both Mediterranean-type diet adherence (compared with low diet score, hazard ratio [HR] for middle diet score was 0.98 [95% confidence

interval {CI}, 0.72-1.33]; the HR for high diet score was 0.60 [95% CI, 0.42-0.87]; $P = .008$ for trend) and physical activity (compared with no physical activity, the HR for some physical activity was 0.75 [95% CI, 0.54-1.04]; the HR for much physical activity was 0.67 [95% CI, 0.47-0.95]; $P = .03$ for trend) were associated with lower AD risk. Compared with individuals neither adhering to the diet nor participating in physical activity (low diet score and no physical activity; absolute AD risk of 19%), those both adhering to the diet and participating in physical activity (high diet score and high physical activity) had a lower risk of AD (absolute risk, 12%; HR, 0.65 [95% CI, 0.44-0.96]; $P = .03$ for trend). **CONCLUSION:** In this study, both higher Mediterranean-type diet adherence and higher physical activity were independently associated with reduced risk for AD.

Comment. Previous studies referenced by the author have shown a Mediterranean-type diet to be associated with lower risk for AD and mild cognitive impairment; and higher rates of physical activity have been associated with lower rates of cognitive decline and dementia. It is therefore not surprising that the authors concluded that both a Mediterranean-type diet and physical activity were independently associated with reduced risk of AD, though magnitude of benefit did not increase with both. Limitations of this study include the bias that individuals who are able to adhere to these healthy behaviors are in better mental health at baseline and therefore less likely to develop AD. Furthermore, these healthier individuals may be more likely to remain in the study cohort, evidenced by the characteristics of those lost to follow up: less educated, higher caloric intake, higher body mass index, and more comorbidities. While the authors took steps to control for these factors, such bias is inherent in observational studies of this type and cannot be completely controlled. The question is whether this bias negates the results of this study and many others that tout the benefits of the Mediterranean-type diet and higher levels of physical activity.

The Mediterranean-type diet has been associated with many health benefits, most notably the reduction of cardiovascular disease (CVD). The Lyon Diet Heart Study showed a 50% to 70% reduction in coronary heart disease (CHD) recurrence including fatal and nonfatal myocardial infarction (MI) and stroke in those adhering to the Mediterranean diet.¹ Similarly, increased physical activity has been associated with many health benefits including but not limited to reduced relative risk of CHD by almost 20%, as demonstrated by the Harvard Alumni Health Study.² The effect of Mediterranean-type diet and physical activity on CVD are not insignificant given that CVD remains the number one cause of death in the United States. Certainly, these findings are relevant to patients with AD as they are typically advanced in age and are demographically the same patient population afflicted by CVD. Furthermore, CVD (specifically cerebrovascular disease) could significantly impact the clinical expression and

degree of cognitive compromise suffered by patients with AD.³ Given these findings, it seems prudent to endorse a Mediterranean-type diet and physical activity as a means to mitigate cognitive decline in AD patients, as well as reduce concomitant disease burden.

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The level of evidence indicated for each study is based on a grading system that evaluates the scientific rigor of the study design, as developed by the US Preventive Services Task Force. A synopsis of the levels is presented below.

Level I	Properly randomized, controlled trial.
Level II-1	Well-designed controlled trial but without randomization.
Level II-2	Well-designed cohort or case-control analytic study.
Level II-3	Multiple time series with or without the intervention (eg, cross-sectional and uncontrolled investigational studies).
Level III	Meta-analyses; reports from expert committees; descriptive studies and case reports.

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